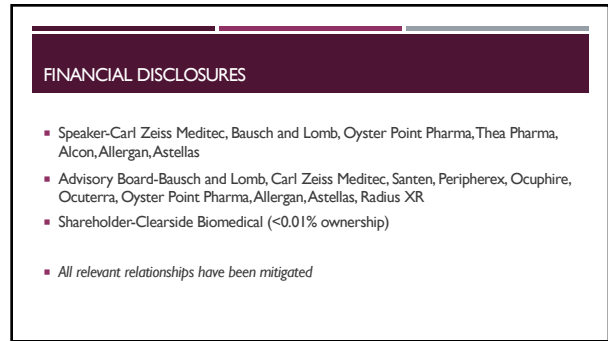
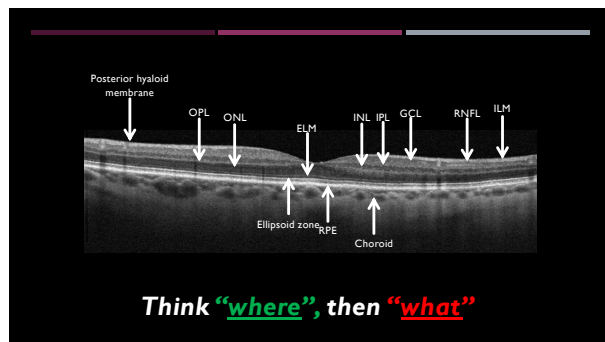




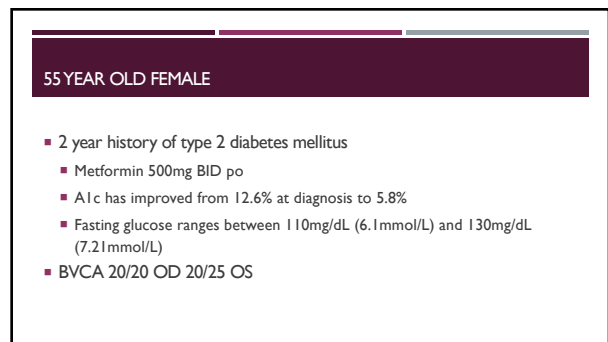
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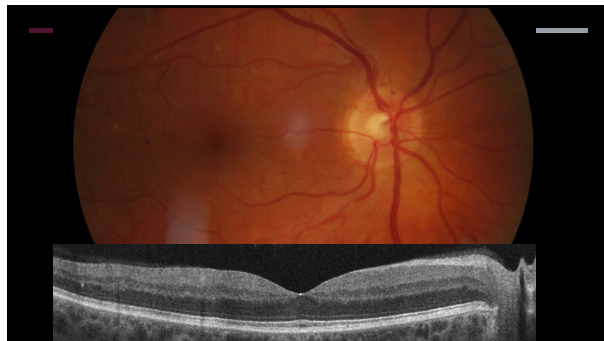
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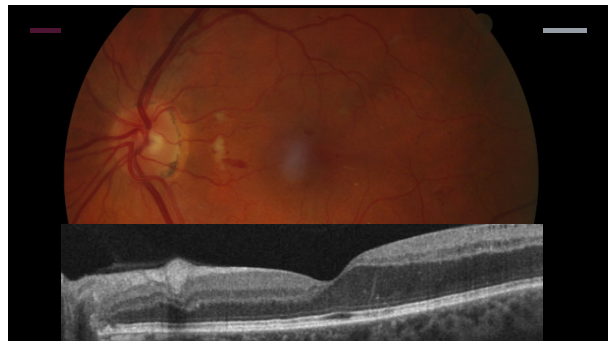
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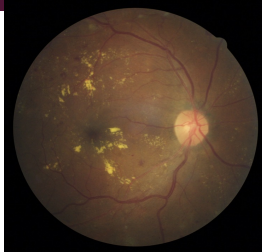
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6

DIABETIC RETINOPATHY

- End organ response to systemic disease
- Multifactorial condition
 - Hyperglycemic component
 - Free-radical formation
 - Oxidative stress
 - Vascular component
 - Inflammation
 - Compromised autoregulation
- Tissue damage to metabolically active sites



7

DIABETIC RETINOPATHY

- Type II: High incidence of DR at the time of presentation
 - Annual exam
 - Insulin-dependent type II patients are considered to be of higher risk
- Type I: No matter how poorly controlled, typically no retinopathy for 5-7 years
 - Examine 5 years after diagnosis—or at age ten, then annually
- Gestational DM
 - Do not seem to have increased risk of DR; no examination recommendation during pregnancy
 - But—for individuals with diabetes who are pregnant:
 - Diabetic retinopathy worsens during pregnancy

8

DIABETIC RETINOPATHY

- Vision loss occurs secondary to:
 - 1) Diabetic macular edema
 - 2) Macular ischemia
 - 3) Proliferative diabetic retinopathy

9

DIABETIC MACULAR EDEMA

- Caused by microvascular occlusion or leakage
- 'CSME' defined by ETDRS
 - Hard exudate within 500 μ m of the center of the macula
 - Hard exudates at or within 500 μ m of the center of the macula with adjacent retinal thickening
 - Retinal thickening of 1DD or larger within 1DD of the center of the macula

10

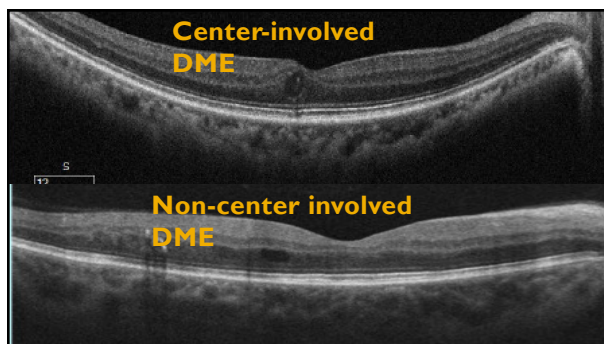


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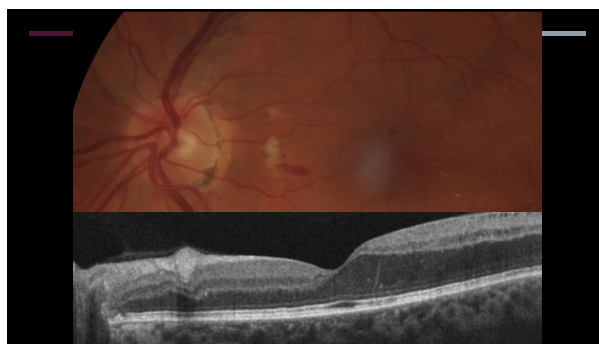
NOW

- Is macular edema present?
- Yes, or no?
 - Sometimes OCT is needed to aid in diagnosis
- If macular edema is present, classify based on OCT findings

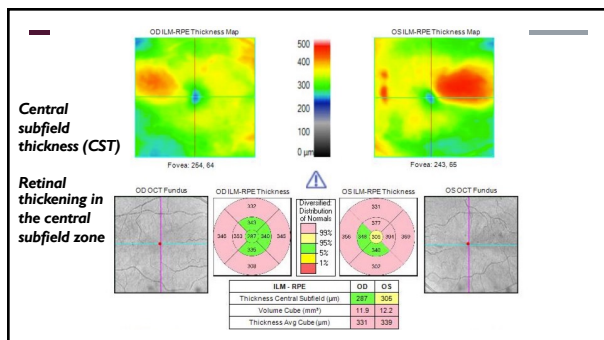
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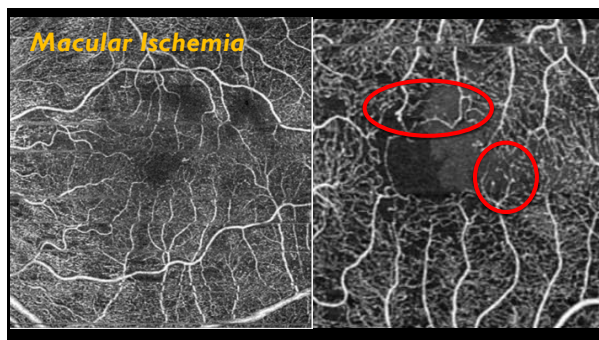
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16

RETINAL VASCULATURE

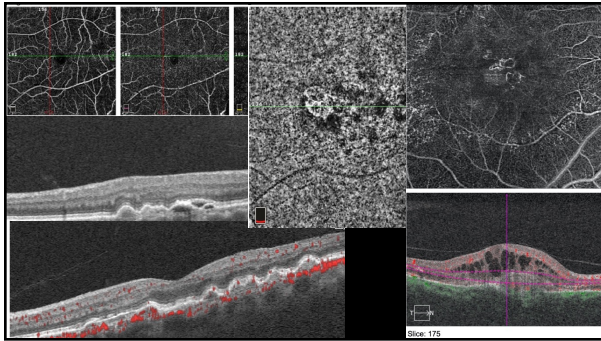
- Retinal capillaries
 - 1) Superficial capillary plexus (GCL-to a lesser extent RNFL)
 - Most affected in artery based conditions (HTN)
 - 2) Deep capillary plexus (INL)
 - Prevenular capillary network
 - Most affected in venous congestive disease (diabetes and RVO)
 - Outer boundary is the outer plexiform layer

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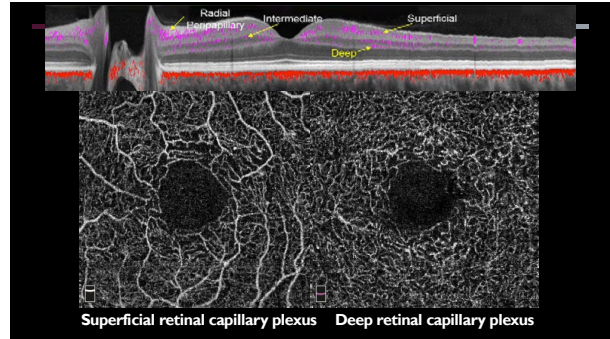
OCT ANGIOGRAPHY

- En face flow formation and cross sectional structural information
- Not a replacement for FA/OCT
 - Provides new information
- Important in diagnosis of NV and macular ischemia

18




19



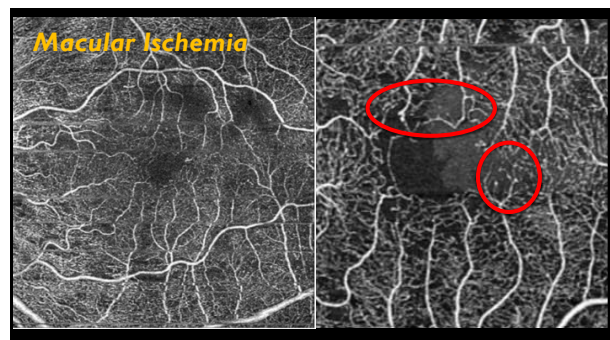
20

Challenges in OCTA

- Static blood flow information
No leakage, pooling or staining
- Small field of view 3x3mm; 6x6mm;
8x8mm with current systems
- Motion artifacts are a big deal
- Sensitivity is a challenge in eyes with pathology
- Quantification of blood flow-not yet



21



22

MACULAR ISCHEMIA

- Vision loss either due to fluid within in the macula or a poorly perfused macula
 - Macular ischemia** in the absence of DME/hemorrhage/exudate
- In healthy vs. diseased eyes:
 - Vessel density decreased with disease severity
 - Flow speed **increases** with disease severity

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VASCULAR ENDOTHELIAL GROWTH FACTOR

- Signaling protein for vasculogenesis and angiogenesis
 - Secreted by RPE cells, pericytes, astrocytes and endothelial cells
- Produced in response to ischemia
 - Ultimately leads to neovascularization
- Anti-VEGF is the typical first line treatment

25

Retinal Disease

Neovascular AMD

(and diabetic eye disease...more generally, retinal vascular disease)

Extracellular VEGF pathways

VEGF-A

VEGF-B

VEGF-C

VEGF-D

PlGF

TKI pathways

TIE2 activation pathways

Integrin pathways

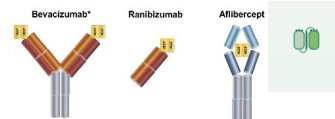
Gene therapy

Unmet needs in management of retinal disease?

26

CURRENTLY AVAILABLE ANTI-VEGF AGENTS

- Ranibizumab (Lucentis)
- Bevacizumab (Avastin)
- Aflibercept (Eylea) & Eylea HD
 - VEGF trap—inhibits VEGF receptor expression
- Brolucizumab (Beovu)
- Faricimab (Vabysmo)



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FARICIMAB (VABYSMO)

Permanent J-code
as of October 1,
2022

- FDA approved January 28, 2022
- Bispecific antibody
 - Targets angiopoietin-2 (Ang-2) and VEGF-A
 - Ang-2 and VEGF work in concert—increases permeability and inflammation
- TENAYA and LUCERNE (nAMD) vs. aflibercept
 - Treated every 3-4 months (after 4 monthly doses)
 - 80% of individuals were able to go 3+ months between treatments in the first year
- YOSEMITE and RHINE (DME)
- Occlusive vasculitis—0.17/10,000 (vs. 5/10,000 endophthalmitis)



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Eylea HD: High Dose Aflibercept (8mg)

PHOTON (DME) and PULSAR (nAMD)

12 and 16 week dosing regimens vs. Eylea x q8weeks

93% (PHOTON) and 83% (PULSAR) maintained q12 weeks or greater

FDA Approval
August 18, 2023

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DOSAGE AND ADMINISTRATION

- Neovascular (Wet) Age-Related Macular Degeneration (nAMD)**
 - The recommended dose for EYLEA HD is 8 mg (0.07 mL of 114.3 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days) for the first three doses, followed by 8 mg (0.07 mL of 114.3 mg/mL solution) via intravitreal injection once every 8 to 16 weeks, +/- 1 week. (2.2)
- Diabetic Macular Edema (DME)**
 - The recommended dose for EYLEA HD is 8 mg (0.07 mL of 114.3 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days) for the first three doses, followed by 8 mg (0.07 mL of 114.3 mg/mL solution) via intravitreal injection once every 8 to 16 weeks, +/- 1 week. (2.3)
- Diabetic Retinopathy (DR)**
 - The recommended dose for EYLEA HD is 8 mg (0.07 mL of 114.3 mg/mL solution) administered by intravitreal injection every 4 weeks (approximately every 28 days +/- 7 days) for the first three doses, followed by 8 mg (0.07 mL of 114.3 mg/mL solution) via intravitreal injection once every 8 to 12 weeks, +/- 1 week. (2.4)

30

COST EFFECTIVENESS OF ANTI-VEGF

- \$2625 aflibercept (8mg/0.07mL)-Eylea HD
- \$2190 faricimab (6mg/0.05mL)-Vabysmo
- \$1850 brolucizumab (6mg/0.05mL)-Beovu
- \$1850 aflibercept (2.0mg/0.05mL)-Eylea
- \$1170 ranibizumab (0.3mg/0.05mL)-Lucentis
- \$70 bevacizumab (1.25mg/0.05mL)-Avastin
- Bevacizumab is a typically the first line anti-VEGF in the USA**

31

Anti-VEGF in DME & DR

DRCRnet Protocol S (2016): Ranibizumab (Lucentis) in PDR non-inferior to PRP

Protocol T (2018) Aflibercept vs. bevacizumab vs. ranibizumab in DME: For VA 20/50 or worse, aflibercept better at improving VA

Protocol V (2019): Center-involved DME (20/25+) no difference in vision at 2 years

32

Anti-VEGF in DME & DR

DRCRnet Protocol AC (2022)

Bevacizumab patients did really well at 2 years—is it reasonable to begin with bevacizumab and switch to aflibercept if “clinically” indicated?

70% of patients met switch criteria; almost all within the first year

Monotherapy was \$12000 more costly than switch

33

Anything other than intravitreal injections?

APX3330 oral tablet for the management of diabetic retinopathy

ZETA-1 Phase 2b trial

Targets apurinic/apurimidinic endonuclease 1 (APE1/Ref-1) protein
= reduction of abnormal new vessel formation (reduces VEGF & VEGF signaling) & inflammation (reduces TNF alpha)

OTT166

DREAM Phase 2 trial
Integrin inhibitor—TOPICAL

34

Anything other than intravitreal injections?

OCS-01

High concentration dexamethasone (topical ophthalmic) for DME

OCS-01 or vehicle 6x daily for 6 weeks, 3x daily for 6 week maintenance phase

No cataract development through 12 weeks

15% IOP increase

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What about eyes without DME?

Panorama

Eylea for patients with moderately severe, or severe NPDR (DRSS)

No macular edema

Sure, patients who received injections showed regression of DR

This makes sense

But, did it result in long term improvement in visual function?

Not assessed.

Protocol W

2 year data

Reduced risk of development of CI-DME and PDR

(16.3% vs. 43.5%)

Average of 8 injections over 2 years

No difference between visual acuity at 2 years

How do you treat patients with very severe NPDR without DME?

United States (n=747)

88.5% A

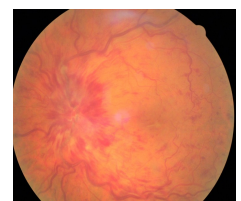
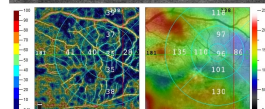
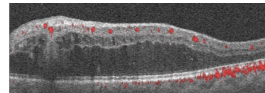
24.9% C

A = Closely monitor retinopathy and encourage systemic glycemic control
B = Consider anti-VEGF in some patients with good sugar control and compliance
C = Consider anti-VEGF in some patients with poor sugar control and/or other risk factors

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RETINAL VEIN OCCLUSION

- Central retinal vein occlusion
- Obstruction at the level of the lamina cribrosa



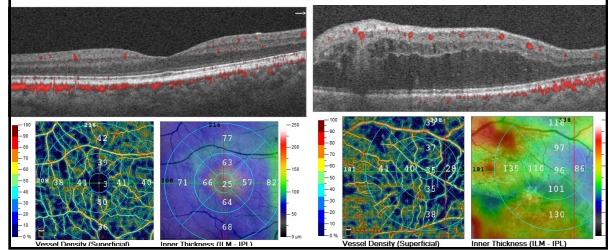
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RETINAL VEIN OCCLUSION

- Arteriosclerosis
 - Loss of elasticity within the vessel wall
 - Arterioles and venules share common adventitia at crossings
 - Venular compression and turbulent blood flow
 - Thrombus formation and occlusion

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What's the status of the fellow eye?



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SCORE2

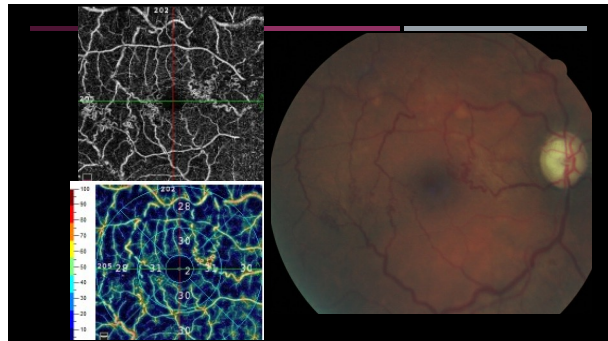
5 year data (April 2022)

No significant difference between Avastin and Eylea

66% had at least one treatment between year 4 and 5

RVO is a chronic disease

41

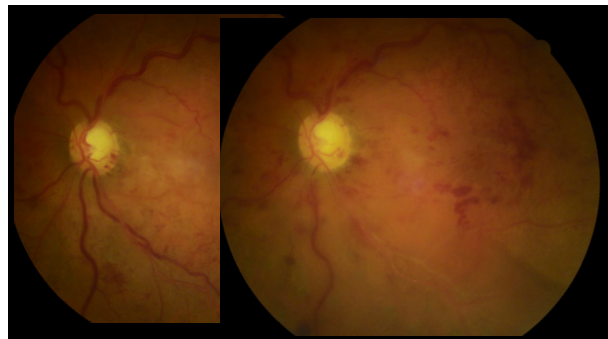


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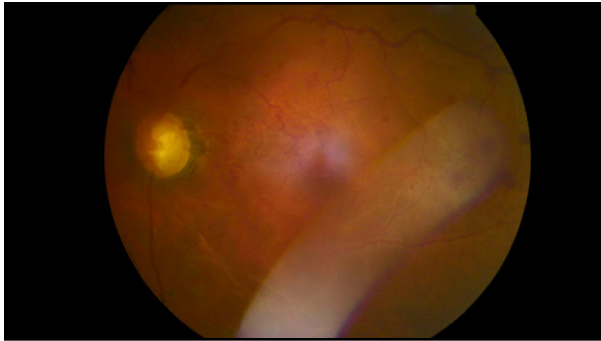
ISCHEMIC CRVO

- Believed that occlusion leads to increased resistance which causes stagnant blood and ischemia
- Leads to PR death, increased cytokine production, increased VEGF
- Anterior and posterior neovascularization
 - Vitreous hemorrhage, anterior segment NV

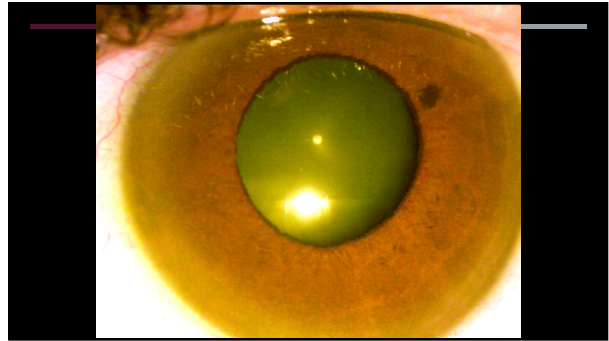
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RIPL & Cardiovascular Disease

Retinal ischemic perivascular lesions (RIPLs)

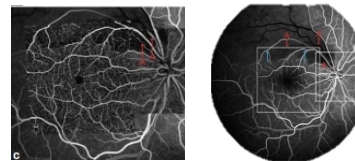
**Generalized marker of cardiovascular disease—
and independently, atrial fibrillation!**

**Markers of retinal ischemia; atrophy at the level
of the inner nuclear layer (deep capillary plexus)**

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BRAO

■ Stroke evaluation on emergent basis—**where is your nearest 24 hour ER
with stroke center?**



Bonnin, Kyriacos, Cognat, Tadayoni J Ophthalmic Vis Res 2018

48

I have discussed elsewhere⁴ why it is irrational to equate retinal artery occlusion with stroke.

Comment on: Retinal vein occlusion and the risk of dementia: A nationwide cohort study

per se. The presence of a particular associated systemic disease does not necessarily imply a cause-and-effect relationship. Thus, the authors' conclusion that "RVO may be a risk factor for dementia" has no scientific validity.

SOHAN SINGH HAYREH, MD, PhD
Department of Ophthalmology & Visual Sciences, College of Medicine,
University of Iowa, Iowa City, Iowa



Re: Biousse et al.: Management of acute retinal ischemia (Ophthalmology. 2018;125:1597-1607)

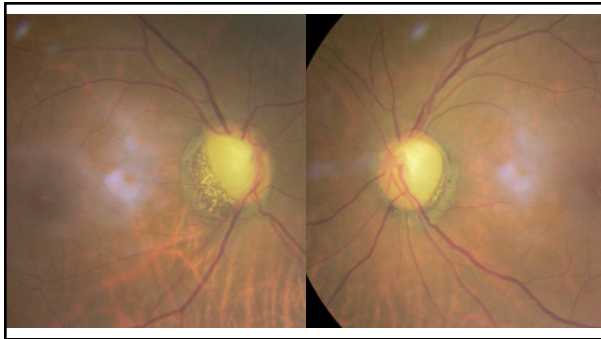
TO THE EDITOR: I was interested to read the article by Biousse et al¹ dealing with the management of acute retinal artery occlusion; this is a repetition of the views dealing with management of acute retinal ischemia they expressed some time ago.² I published an article on the same subject,³ discussing a concept opposite to that of Biousse et al.^{1,2} Our different views on the topic likely relate to coming at this from the viewpoint of our different specialties, which provide different perspectives on the subject. I have been dealing with acute retinal artery occlusion for >50 years and my studies on retinal artery occlusion are the largest studies reported (>500 cases). Biousse et al, being neuro-ophthalmologists and neurologists, have a neurologic bias. In support of their argument, they cite opinions expressed

49

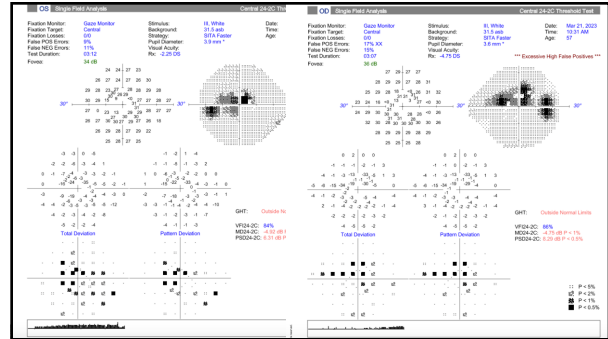
58 YEAR OLD BLACK FEMALE

- History of medically managed POAG OU
 - Latanoprost QHS OU, brimonidine-timolol BID OU
- History of recurrent anterior scleritis (alternating, bilateral)
 - 1-2 flares per year; 6 flares in 2020
 - Resolve with Durezol QID & oral ibuprofen (up to 2400mg daily)
- ...she is a steroid responder with peak pressure of 34mmHg

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Black Box Warnings

Cardiovascular Thrombotic Event
NSAIDs incr. risk of serious and potentially fatal cardiovascular thrombotic events, incl. MI and stroke, risk may occur early in tx and may incr. w/ duration of use; contraindicated for CABG postop pain

GI Bleeding, Ulceration, and Perforation
NSAIDs incr. risk of serious and potentially fatal GI adverse events incl. bleeding, ulcer, and stomach or intestine perforation; GI events may occur at any time during use and w/o warning sxs; elderly pts and pts w/ h/o PUD or GI bleeding at greater risk for serious GI events

Product	STRENGTH (IBUPROFEN mg/TABLET)	SINGLE ORAL DOSE	MAXIMUM DAILY DOSE (1200 mg)
MOTRIN® 200 mg (REGULAR STRENGTH)	200mg	1 or 2 tablets	6 tablets
MOTRIN® 300 mg (EXTRA STRENGTH)	300mg	1 tablet	4 tablets
MOTRIN® 400 mg (SUPER STRENGTH)	400mg	1 tablet	3 tablets

Adults and children 12 years and over: The single oral dose may be taken every 4-6 hrs. **Do not take more than the maximum daily dose (1200 mg in 24 hours)** unless advised by a doctor.

Oral NSAIDs-OTC vs. Rx

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Adult Dosing

Dosage forms: CAP: 200 mg; TAB: 100 mg, 200 mg, 400 mg, 600 mg, 800 mg; CHEWABLE: 50 mg, 100 mg; SUSP: 100 mg per 5 mL, 50 mg per 1.25 mL.

osteoarthritis
[300-800 mg PO tid-qid]
Max: 3200 mg/day; Info: use lowest effective dose, shortest effective tx duration; give w/ food if GI upset occurs

rheumatoid arthritis
[300-800 mg PO tid-qid]
Max: 3200 mg/day; Info: use lowest effective dose, shortest effective tx duration; give w/ food if GI upset occurs

for anti-inflammatory uses (off-label)
400-800 mg PO bid-tid x 1-14 days
Max: 2400 mg/day; Info: use lowest effective dose, shortest effective tx duration; give w/ food if GI upset occurs

pain, mild-moderate
400 mg PO q4-6h prn
Max: 2400 mg/day; Info: use lowest effective dose, shortest effective tx duration; give w/ food if GI upset occurs

What is the maximum daily dosage?!

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TOPICAL STEROIDS IN ANTERIOR SCLERITIS?

- Difluprednate 0.05% ophthalmic emulsion
- Difluorinated prednisolone derivative
 - About twice as potent as prednisolone acetate
 - Enhanced drug penetration
- On label for the treatment of inflammation and pain associated with ocular survey & treatment of endogenous anterior uveitis
- Preserved with sorbic acid 0.1%; utilizes Durasite vehicle

55

Effectiveness of Difluprednate for the Treatment of Anterior Scleritis

PAULINA LIBERMAN, BRYN M. BURKHOLDER, JENNIFER E. THORNE, AND MEGHAN K. BERKENSTOCK

• **CONCLUSIONS:** Difluprednate alone may effectively treat non-infectious anterior scleritis with a tolerable side effect profile. (Am J Ophthalmol 2022;235: 172–177. © 2021 Elsevier Inc. All rights reserved.)

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NOW WHAT?

- Targeted (useful) review of systems:
 - Respiratory: no dyspnea, wheezing
 - CV: no palpitations, arrhythmia, chest pain, leg swelling
 - Musculoskeletal: no joint discomfort
 - Integumentary: no rash, hair loss, mucosal ulceration, bruising, lesions

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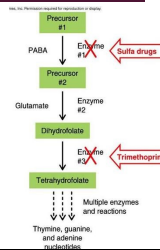
BASIC SEROLOGICAL EVALUATION

- Complete metabolic panel (14)
- Complete blood count with differential & platelets
- Erythrocyte sedimentation rate
- C-reactive protein
 - ***43.5mg/dL (reference range <8.0mg/L)

58

RHEUMATOLOGY CONSULTATION

- Advocate for treatment.
- Serological evaluation for inflammatory arthritis and vasculitis
- ...
- Diagnosis "Elevated CRP"
 - Methotrexate 15mg po weekly, folic acid 1mg daily
 - Antimetabolite which inhibits dihydrofolate reductase (second step of folic acid production)



60

Where are we now?

IOP is 12mmHg OD and OS; she is tolerating treatment well

Visual fields and optic discs are stable

CRP still elevated—and actually nearly unchanged; but no flare ups since beginning therapy

Lab Results	Component	Value
SEDRATE		19
Lab Results	Component	Value
CRP		40.3 (H)

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BOTTOM LINE

- Successful, long-term outcomes of ocular conditions resulting from systemic disease begins with:
 - A careful description of clinical ocular and ancillary findings
 - General medical knowledge and understanding of pathophysiology
 - Coordination and ongoing communication with comanaging providers

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THANK YOU!

- Jessica.steen@gmail.com
- 480.289.0613



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